Tartrate-like Ligands in the Asymmetric Epoxidation†

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Three "tartrate-like" ligands, (3*R*,4*R*)-diisopropyl 3,4-dihydroxyadipate (**3**), (2*S*,4*S*)-diisopropyl 2,4-dihydroxyglutarate (**4**), and (2*S*,5*S*)-diisopropyl 2,5-dihydroxyadipate (**5**) were synthesized with the aim of gaining further insight into the nature and composition of the asymmetric epoxidation catalyst. Both **3** and **4** appear able to form and maintain a dimeric (2:2) Ti–ligand complex analogous to Ti–tartrate in the presence of competitive alcohol binders, but **5** seems to give a mixture of complexes. In reactivity screens, Ti–**3** is a very sluggish and nonselective epoxidation catalyst; Ti–**4** mimics Ti–tartrate in the epoxidation of primary allylic alcohols (>93% ee), but is ineffective as a kinetic resolution catalyst; Ti–**5** is only weakly selective, implying the presence of more than one active epoxidation catalyst. The relationships between catalyst intramolecular fluxional equilibration, torsional ring strain, alkoxide exchange rate, reaction rate, and face selectivity are explored.

Introduction

The titanium–tartrate mediated asymmetric epoxidation of prochiral allylic alcohols by alkyl hydroperoxides was introduced in 1980.[1a] Due to a combination of substrate generality, excellent enantioselectivity and practicality,[2] it has already enjoyed wide application in organic synthesis.[3] The concomitant discovery that the Ti–tartrate system is also effective for kinetic resolution[1b] of racemic secondary allylic alcohols further increased its synthetic utility and became a key consideration in the mechanistic investigations that followed.[4]

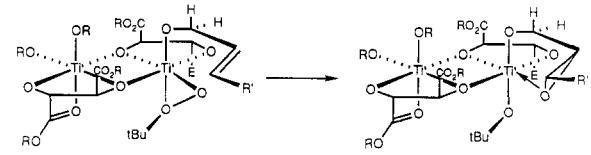
Since the initial discovery, there has been intense interest in two related aspects of the system: the structure of the active catalyst and the mechanism of the reaction. Crystallographic,[5] spectroscopic, and molecular weight data[4] point to the C_2-symmetric tartrate-bridged dimer **1** (Figure 1) as the *major* species in 1:1 titanium alkoxide–dialkyl tartrate solutions. Further, mechanistic findings strongly imply that the major species (**1**) and the catalytically active species are one and the same.[4]

In the roughly octahedral, reactive catalyst species, the allylic alkoxide is believed to be bound trans to the coordinated ester carbonyl and the *tert*-butyl peroxide cis to the carbonyl. There is evidence that subsequent carbonyl dissociation allows bidentate coordination of the alkyl peroxide as shown in Scheme I. Finally, S_N2-type attack of the olefin π-bond along the O–O bond axis results in rate-determining oxygen atom transfer (Scheme I).

The source of enantioselection in the asymmetric epoxidation is still not completely understood. It is believed, however, that a combination of steric and electronic effects is involved which influences the possible reactive allylic alkoxide conformations such that only one appears to be greatly favored.[6]

The rapid assembly of 1:1 Ti–tartrate mixtures into a thermodynamic well and the high stereoselectivity in both the asymmetric epoxidation and kinetic resolution reactions demanded an investigation into the many variables through which the catalyst operates. Certainly one of the key variables is the chiral ligand itself, on which both the catalyst assembly and the asymmetric induction depend. A rather extensive ligand study has been undertaken,[4a,7] the results of which lay the groundwork for a better understanding of the system and of Ti–alkoxide chemistry in general.[8] This paper presents a brief overview of some of the ligand investigations that have helped shape our structural and mechanistic thinking and then focuses on three ligands which were prepared specifically for this system, based on the knowledge gained from these previous studies.

Scheme I



Assessing structure–activity relationships with complexes of this kind is made especially challenging by the dynamic nature of these systems, which, along with their many coordination options, renders them capable of existing as a variety of species in rapid equilibrium. This dynamism usually makes the structural details of the assembly very difficult to determine, which in turn means that conclusions on the origins of the reactivity/selectivity patterns must be regarded as tentative. By examining ligands which are structurally similar to those which give a known metal–ligand structure, we seek to minimize such

† This paper is dedicated to our colleague Professor Frederick D. Greene in appreciation of his years of service as Editor of *The Journal of Organic Chemistry*.

(1) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(2) This is now particularly true with the new sieves modification which renders the reaction truly catalytic (ca. 5 mol %) in Ti–tartrate: (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(3) (a) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 7, p 193. (b) Pfenninger, A. *Synthesis* **1986**, 89.

(4) Most of the work done in this area is contained in a review and further elaborated upon in two papers in preparation: (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8, p 247. (b) Finn, M. G.; Sharpless, K. B., manuscript in preparation. Woodard, S. S.; Finn, M. G.; Sharpless, K. B., manuscript in preparation. The reader should refer to these for a detailed examination of this topic.

(5) For X-ray crystal structures of several catalyst analogues, see: Williams, I. D.; Pedersen, S. F.; Sharpless, K. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 6430. Pedersen, S. F.; Dewan, J. C.; Eckman, R. R.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1279.

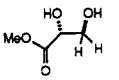
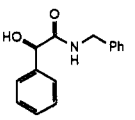
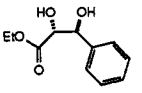
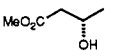
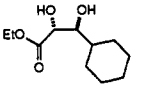
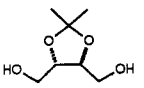
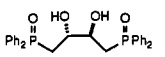
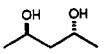
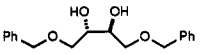
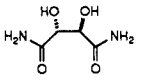
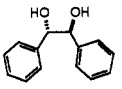
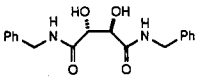
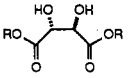
(6) The four most likely allylic alkoxide conformations (of which only one is favored by the empirical data) are examined in detail in ref 4a.

(7) For an examination of several ligands not discussed here, see: (a) Hawkins, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1987**, 2825. (b) Carlier, P. R.; Sharpless, K. B., submitted for publication in *J. Org. Chem.*

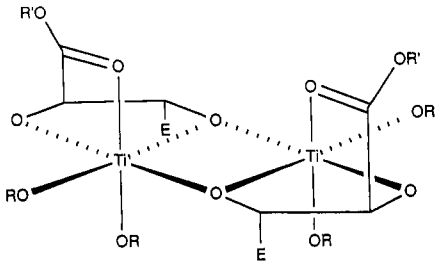
(8) For a general treatment of Ti alkoxide chemistry, see: Bradley, D. C.; Mehrotra, R. C.; Gaur, D. P. *Metal Alkoxides*; Academic Press: New York, 1978. Chisholm, M. H.; Rothwell, I. P. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R., McCleverty, J. A., Eds.; Pergamon Press: New York, 1987; Vol. 2, Chapter 15.3.

0022-3263/89/1954-2826$01.50/0

Table I. A Selection of the Ligands Used for the Epoxidation of (*E*)-2,3-Diphenyl-2-propenol by Ti(OiPr)$_4$ and TBHP at 0 °C in CH_2Cl_2[a]

entry		% ee	entry		% ee
1		0	8		35 (*S*)
2		4 (*S*)	9		80 (*S*)
3		5 (*R*)	10		>98 (*S*)
4		23 (*S*)	11		0
5		13 (*S*)	12		12 (*R*)
6		5 (*R*)	13		19 (*R*)
7		0	14		96 (*S*)
			15		>98 (*S*)

[a] Ratios of Ti:ligand are 1:1 or 1:1.2. Configurations at C-2 of the product epoxy alcohols are shown in parentheses next to the % ee.



1

Figure 1.

uncertainties. By this analogy, ligands for the asymmetric epoxidation catalyst which are "tartrate-like" in structure might be expected to form titanium complexes similar to the parent structure 1, thereby making their reactivity/stereoselectivity effects more informative.

Results and Discussion

Ligand Survey. Initial studies on the epoxidation system had focused on a variety of ligands which were deemed likely to bind to titanium, some of which bore only superficial resemblance to tartrate. A representative sampling of the more than 50 ligands examined[4a] is shown in Table I.

Simple homochiral α-hydroxy esters and amides (entries 1, 2) and β-hydroxy esters (entry 3) gave very low stereoselection in the screen, demonstrating that one ester and one carbinol are not sufficient to generate an enantioselective catalyst. Homochiral 1,4-, 1,3-, and 1,2-diols (entries 4–7) are also poor ligands in the epoxidation, suggesting that a diolate alone is likewise not sufficient. Incorporating three of the four functional groups of tartrate into the ligand (entries 8–10) does give an enantioselective catalyst, particularly when the "fourth" slot is taken up by more sterically demanding groups, but results in less effective kinetic resolution of racemic secondary allylic alcohols.[9] Tartrate analogues in which the esters are replaced by methylene alkoxy or methylenephosphine oxide groups (entries 11 and 12) were ineffective (generally < 15% ee) despite the possibility that these dative coordinators might behave in a manner similar to the tartrate ester carbonyls. Replacing the esters with amides affords epoxide with anywhere from 19 to 96% ee (entries 13 and 14).[10]

Clearly, both a glycolate and at least one ester or amide carbonyl are essential for obtaining high enantioselectivity in the reaction. This is consistent with the ground-state model 1, which suggests that only tridentate coordination of the tartrate ligand is required and that the unbound carbonyl is not essential for formation of an active species. Still, the uncoupling of face selectivity and kinetic resolution of entries 9 and 10 suggests that *all four* tartrate functional groups may be playing a role in the latter process.

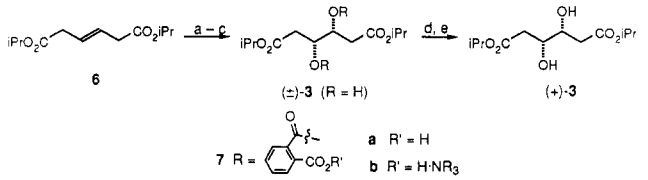
The next logical question revolved around the arrangement of these four groups in the tartrate skeleton (and by association, in a 2:2 complex); hence, three C_2-symmetric homochiral tartrate-like ligands were envisioned which incorporate all four functional groups intrinsic to tartrate, but which also contain one or more methylene units interspersed among them.

Diisopropyl 3,4-dihydroxyadipate (3) would, in theory, allow the five-membered Ti–glycolate rings of 1 to stay intact but would give the ester carbonyls more flexibility

(9) For example in the kinetic resolution of (±)-(*E*)-1-cyclohexyl-2-buten-1-ol (14), a 1:1 Ti–L catalyst derived from the ligand depicted in entry 9 showed k_{rel} 1.2, that from entry 10 gave k_{rel} 6.1, and diethyl tartrate (DET) gave k_{rel} 36.[1b] Note that the term k_{rel} represents the relative rate difference for the reaction of the two substrate enantiomers.

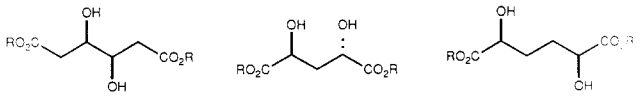
(10) The 2:2 Ti–ligand complex derived from entry 14 has been analyzed by X-ray analysis[5] and provides one of the bases for the proposed structure 1.

Scheme II[a]



[a] (a) Catalytic OsO_4, NMO, acetone, H_2O; (b) phthalic anhydride, pyr; (c) cinchonidine, CH_2Cl_2; (d) H^+, EtOAc; (e) $Ti(OiPr)_4$, iPrOH.

and greater reach than in tartrate, a characteristic which we anticipated would lead to stronger ester carbonyl binding and perhaps greater stabilization of the dimeric ground state.



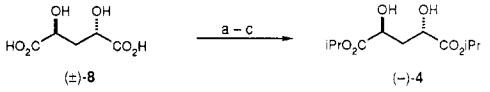
Diisopropyl 2,4-dihydroxyglutarate (**4**) would address the possibility of forming bridging six-membered Ti–glycolate rings analogous to the five-membered Ti–tartrate rings, a prospect considered feasible due to the prevalence of this chelate size in Ti alkoxide coordination chemistry[8] and the encouraging fit noted in the models.

Diisopropyl 2,5-dihydroxyadipate (**5**) would force the issue to an even greater extent, demanding two seven-membered Ti diolate rings in order to maintain the proposed dimeric Ti_2O_2 framework. Some difficulty was expected in maintaining this structure as there is no literature precedent for seven-membered Ti(IV) diolate rings. Nevertheless, an examination of molecular models indicated that should this assembly occur, it could, like tartrate, benefit from the stabilization afforded by dative coordination of at least one of the carbonyls.

The diisopropyl esters of these ligands were chosen due to their low water solubility, the fact that they provided an attractive NMR handle in spectroscopic studies,[11] and because potential transesterifications with reactant allylic alcohol or product epoxy alcohol were expected to be slow, particularly at normal epoxidation reaction temperatures (0 to −20 °C).

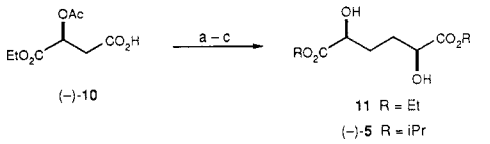
Ligand Syntheses. (3*R*,4*R*)-Diisopropyl 3,4-dihydroxyadipate (**3**) was prepared from diisopropyl 3-hexenedioate (**6**) by osmium-catalyzed dihydroxylation[12] to (±)-**3**, resolution of the derived bis phthalate half-ester **7a** as the bis cinchonidine salt **7b**, and straightforward removal of the alkaloid (by acidification) and the phthalate groups (by Ti-catalyzed[13] transesterification) (Scheme II). Stoichiometric asymmetric dihydroxylation of **6** using dihydroquinidine *p*-chlorobenzoate as chiral auxiliary[14] afforded diol of 71% ee,[15] but attempts to recrystallize this

Scheme III[a]



[a] (a) 1 equiv of brucine, acetone, H_2O (to **9**); (b) CH_2N_2; (c) $Ti(OiPr)_4$, iPrOH.

Scheme IV[a]



[a] (a) Na, EtOH; (b) Kolbe electrolysis; (c) $Ti(OiPr)_4$, iPrOH.

to optical purity were unsuccessful.

(2*S*,4*S*)-Diisopropyl 2,4-dihydroxyglutarate (**4**) was prepared by resolution of the racemic dihydroxy diacid **8**[16] as the mono brucine salt **9**, treatment of the salt with diazomethane to form the dimethyl ester, and transesterification[13] (Scheme III). The absolute configuration was correlated as the derived barium salt.[17]

(2*S*,5*S*)-Diisopropyl 2,5-dihydroxyadipate (**5**) was prepared by Kolbe anodic oxidative coupling[18] of the sodium salt of **10** (prepared in two steps from (*S*)-(−)-malic acid[19]), followed by transesterification of the diethyl ester **11**[20] (Scheme IV).

Spectroscopy and Molecular Weight. Molecular weight determinations of 1:1 mixtures of $Ti(OiPr)_4$ and ligand **3** (Ti–**3**),[21] using the isopiestic Signer method,[22] indicate a molecularity of 2, meaning that the resulting complexes are dimeric. The corresponding spectroscopy in $CDCl_3$ and CD_2Cl_2 suggest that there is one major species in solution. The ^1H NMR spectrum shows what appear to be resonances for two inequivalent Ti–isopropoxide methines, ligand methines, and isopropyl ester methines. The distinct signals contrast with the averaged signals observed with Ti–tartrate because Ti–**3**, with its increased carbonyl–metal accessibility, does not appear to partake as readily in the "fluxional interconversion" process[23] postulated for **1**. Only upon warming is broadening

(11) Broad, unresolved signals are often observed for Ti alkoxide NMR spectra due to the facility of ligand exchange on the ^1H and ^{13}C NMR time scales, and the isopropyl methine heptets are normally more first-order in appearance than, for example, the diastereotopic methylenes of the ethyl esters, which tend to be much more complex and broadened when complexed to titanium.

(12) Van Rheenan, V.; Kelly, R. C.; Cha, D. F. *Tetrahedron Lett.* **1976**, 1973.

(13) Seebach, D.; Hüngerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.

(14) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

(15) To date, there has been no exception to the empirically determined rule that the oxygens are delivered to the *re,re* face of trans-symmetrical olefins when dihydroquinidine esters are used as chiral modifiers (for example, *trans*-3-hexene gives (3*R*,4*R*)-(+)-3,4-dihydroxyhexane, also in approximately 70% ee, by this stoichiometric osmylation procedure). Thus, although the absolute configuration of the homochiral material obtained by the resolution procedure has not yet been rigorously proven, it is assigned as 3*R*,4*R* with some measure of confidence by comparison of the sign of its optical rotation to that of the product obtained from the stoichiometric asymmetric osmylation.

(16) (a) Ingold, C. K. *J. Chem. Soc.* **1921**, 322. (b) It is noted that the *dl* and meso assignments for separated samples of **8** given by Ingold are in error and were later corrected by several groups: Roth, B. M.; Schaltegger, H. *Helv. Chim. Acta* **1964**, *47*(6), 1621. Velichko, F. K.; Vinogradova, L. V.; Amriev, R. A.; Freidlina, R. Kh. *Dokl. Akad. Nauk SSSR* **1970**, *194*, 1080. Also see ref 17.

(17) Benoiton, L.; Winitz, M.; Birnbaum, S. M.; Greenstein, S. P. *J. Am. Chem. Soc.* **1957**, *79*, 6192.

(18) Brettle, R.; Latham, D. W. *J. Chem. Soc. C* **1968**, 906.

(19) Shiuey, S. J.; Partridge, J. J.; Uskoković, M. R. *J. Org. Chem.* **1988**, *53*, 1040.

(20) Spectral analysis showed the product of the electrolysis to be almost completely diethyl 2,5-dihydroxyadipate, with no discernible presence of the expected mono or diacetoxy derivatives,[18] presumably due to transesterification by NaOEt during the electrolysis.

(21) Unless noted otherwise, all molecular weight measurements and spectra were taken of complexes in which the released iPrOH was azeotropically removed by three evaporation cycles with CH_2Cl_2 (see the Experimental Section).

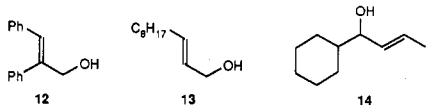
(22) Clark, E. P. *Ind. Eng. Chem., Anal. Ed.* **1941**, *13*, 820.

due to exchange observed. The ^{13}C NMR and IR spectra suggest the presence of bound and unbound carbonyls, and the former shows resonances for only one adipate molecule and two isopropoxides, which in concert with the complex's molecularity supports a C_2-symmetric structure. When the released 2 equiv of iPrOH (used as a rough model for substrate allylic alcohols) are not removed from the mixture, the majority of the spectrum remains unchanged, but the two Ti–isopropoxide peaks are severely broadened, indicating facile exchange of these particular ligands at room temperature. In total, these findings suggest that a C_2-symmetric 2:2 complex analogous to **1** is forming in solution, the core of which is structurally stable to free alcohol.

Like Ti–**3**, the molecular weight determination of the 1:1 Ti:ligand **4** mixture (Ti–**4**) also suggests a dimer. The corresponding NMR and IR spectroscopy is strikingly similar to that of tartrate, exhibiting almost superimposable spectra (where appropriate), down to the unusual low-frequency (ca. 1640 cm^{-1}) C=O IR band.[24] The only noticeable difference between the two is the presence of a minor amount (5–10%) of free $Ti(OiPr)_4$, which appears to originate from a small degree of disproportionation of the major Ti–**4** species, the partner of which is hidden among the other signals. Taken together, the molecular weight and spectroscopic data provide compelling evidence for assigning the Ti–**4** complex as a 2:2 species structurally analogous to **1**.

The spectroscopy of a 1:1 mixture of $Ti(OiPr)_4$ and ligand **5** (Ti–**5**) is more difficult to interpret. The ^1H NMR is broadened, and decoupling experiments have established what appear to be at least two different species in solution, with a small amount of free $Ti(OiPr)_4$. This amount increases when the 2 equiv of released iPrOH are not removed, and the spectra become even more complex. The IR indicates that there are at least two different bound and two different unbound ester carbonyls. The ^{13}C NMR, on the other hand, shows only one obvious carbonyl signal, shifted much further downfield (ca. 12 ppm from the free ligand) than in **1**, Ti–**3**, or Ti–**4** (all of which show a shift in the range of 1–6 ppm). We attribute this to a different Ti–ligand binding mode for which only one signal is observed presumably due to averaging on the ^{13}C NMR time scale.[25] The observed molecularity of 1.4–1.6 seems to support an assembly profile substantially different from that seen with **1**, Ti–**3**, and Ti–**4**.

Reactivity. With the possibility that **3** and **4** form 2:2 Ti:L complexes similar to **1** and that **5** gives something less readily defined, the reactivity profiles of these complexes were investigated. As test substrates, (*E*)-2,3-diphenyl-2-propenol (**12**) and (*E*)-2-undecenol (**13**) were tested for asymmetric induction in epoxidations with TBHP, and (±)-(*E*)-1-cyclohexyl-2-buten-1-ol (**14**) was tested for kinetic resolution.



In light of the encouraging spectroscopic profile exhibited by Ti–**3**, the epoxidations of **12** and **13** (Table II) are surprisingly sluggish compared to tartrate (>34 h vs <1 h) and give *racemic* epoxy alcohol product for **12** and <20% ee for **13**. The system employing Ti–**4**, on the other hand, proceeds at a rate similar to tartrate (<4 h) and gives ≥93% ee for both of the primary test substrates. In contrast to these more extreme results, Ti–**5** demonstrates weak enantioselection with the primary allylic alcohol substrates (10–28% ee), also exhibiting a slow reaction rate, but one that is faster than Ti–**3**.[26]

Despite the wide selectivity extremes demonstrated with primary allylic alcohols, *all three* Ti–ligand systems show pronounced ineffectiveness as kinetic resolution catalysts for **14** (Table II). Using ca. 0.60–0.65 equiv of TBHP, Ti–**3** is again extremely slow, giving only 1% conversion after 4 h at −20 °C and requiring warming to room temperature to proceed at a practical rate. On the other hand, both Ti–**4** and Ti–**5** (as well as $Ti(OiPr)_4$) proceed to give complete consumption of the oxidant (58–65% conversion) within 4 h.[27]

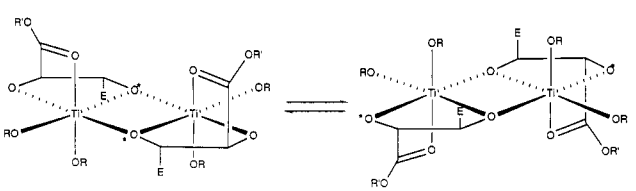
Conclusions

The potential complexity of these metal–ligand systems makes it difficult to provide definitive answers to the many questions one might like to raise about them. Nevertheless, some hypotheses and conclusions are presented below with the anticipation that they will provide an impetus for further work.

The data obtained for ligand **3** presents quite a puzzle. The Ti–**3** catalyst shows four important traits: (1) fast isopropoxide exchange; (2) slow fluxional interconversion; (3) slow epoxidation rate; and (4) low face selectivity. Assuming a structure analogous to **1**, there is an apparent contradiction in the observation that the epoxidation rate is slow when the metal is clearly able to undergo rapid alkoxide exchange.

For the parent Ti–tartrate system, we have assumed that isopropoxide exchange, epoxidation rate, and fluxional interconversion[23] of the catalyst structure are all dependent on dissociation of the bound ester carbonyl. The isopropoxide exchange is thought to be facilitated by opening of a coordination site for dative binding of the alcohol. Epoxidation is contingent upon activation of the oxidant by coordination of both oxygen atoms of the bound alkyl peroxide,[28] which is facilitated by dissociation of the carbonyl for steric (by creation of a vacant ligand site)[29] and

(23) In this degenerate fluxional interconversion, two dimeric Ti–tartrate conformations rapidly interconvert (below), presumably via the intermediacy of a 10-membered ring. Asterisks delineate the movement of the atoms. See ref 4a for a more thorough discussion.



(24) This band is attributed to a carbonyl binding mode that is almost unique to the Ti–tartrate catalyst **1**. With the exception of **4**, only tartrate exhibits this IR stretch on binding to titanium.

(25) The only other instance in which we observed such a substantial downfield ester carbonyl shift on binding to titanium was in an examination of secondary and tertiary monobasic α-hydroxy esters such as ethyl lactate and isopropyl 2-hydroxyisobutyrate, which form monomeric 1:2 complexes in solution: Finn, M. G.; Burns, C. J.; Sharpless, K. B., unpublished results.

(26) In each case where a nonracemic epoxy alcohol product was obtained, the observed enantiofacial selectivity was the same as that of the analogous tartrate ligand (e.g., (2*S*,4*S*)-**4**, (2*S*,5*S*)-**5**, and (2*S*,3*S*)-DET all give epoxide with the 2*R* configuration, while (3*R*,4*R*)-**3** gave product with the 2*S* configuration (for **13**).

(27) Note that the kinetic resolution using **1** as catalyst slows down dramatically near 55% conversion, affording recovered allylic alcohol in >96% ee.[1b]

(28) Bach, R. D.; Wolber, G. J.; Coddens, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 6090.

(29) In **1**, the 5-membered Ti diolate ring's ability to flex to a different conformational pucker brings the unbound carbonyl away from the coordination site and eliminates potential steric problems for oxidant chelation.

electronic (by increasing the Lewis acidity of the metal center) reasons. Lastly, the fluxional interconversion process obviously also involves carbonyl dissociation, since bound and unbound ester groups are exchanged.[30] In spite of the system's thermodynamic preference for 1, the dimer apparently experiences a significant tension between the metal's demand for the additional electron density available through binding of the carbonyl, and the strain that this coordination then introduces.[31] It seemed possible that this tension was expressing itself by inducing rapid carbonyl dissociation, which was then prompting rapid fluxional equilibration on the one hand, and exchange, oxidant chelation, and reaction on the other. With the results obtained using ligands 3, 4, and 5 we hoped to learn more about the apparent interdependence between angle strain, carbonyl dissociation, fluxional interconversion, ligand exchange, and reaction rate.

The observation of fast exchange but slow reaction and slow fluxional interconversion in Ti–3 would seem to undermine the idea that these processes are all interdependent and thus requires an attempt at explanation.

One scenario focuses on the more favorable coordination geometry of the ester carbonyl in Ti–3 (vs 1) and the concurrent decrease in angle strain that the pair of [2.2.2] bicyclic ring systems affords. This decrease in strain is presumably manifested by a greater likelihood that the carbonyl will remain bound. Inability to dissociate the carbonyl[32] on a reasonable time scale would certainly explain the slow rate of fluxional interconversion.[30] If the fast isopropoxide exchange and slow epoxidation rate of Ti–3 are both to be consistent with a more tightly bound carbonyl, a modification of our mechanism is required: these two processes must not be equally dependent on carbonyl dissociation. We focus first on the alcohol/alkoxide exchange reaction.

Although four- and five-coordinate Ti alkoxide complexes are assumed to undergo ligand exchange in most cases by an associative exchange mechanism,[8] such a mechanism is considered less likely when the metal is six-coordinate due to the steric constraints about the relatively small titanium atom. Instead, a dissociative mechanism is often invoked, in which the most weakly bound donor, in this case the carbonyl, is released prior to coordination by the incoming alcohol. To argue that the carbonyl is bound more strongly in Ti–3 than in the Ti–tartrate structure 1 would seem to require that the rapid isopropoxide exchange proceed through a nondissociative mechanism, implying a seven-coordinate, associative pathway.

Bidentate coordination of the bound alkyl peroxide without predissociation of the ester carbonyl would also give rise to a heptacoordinate intermediate. While such η^2-coordination may occur reversibly in the ground state, we believe that it may not be a part of the productive epoxidation event, for two reasons. First, when the carbonyl is bound, the Lewis acidity of the titanium atom is reduced. Thus the η^2-alkyl peroxide would be less active toward epoxidation. Secondly, for steric reasons we have proposed that epoxidation occurs upon binding of the second alkyl peroxide oxygen atom exclusively at the ligand site vacated by the carbonyl. Other binding sites are disfavored (η^2-TBHP involves what amounts to coordination of a neopentyl center). However, attack of free alcohol for ligand exchange, being less sterically demanding, could occur at other positions.

It is also possible for the bound ester carbonyl of Ti–3 to be more labile to dissociation (using the extra CH_2 spacer to allow the carbonyl freedom of rotation away from the metal center) and reassociation such as postulated for Ti–tartrate. This would then explain the rapid isopropoxide exchange (by the normal dissociative mechanism) but would require a different explanation for the slow reaction rate (since now the oxidant is presumably able to become activated by chelating η^2) and for the slow fluxional interconversion (again assuming that carbonyl dissociation is involved in an integral way).[30] This different explanation might have less to do with the difference in angle strain associated with the C=O binding between 1 and Ti–3 and more to do with the second significant difference between tartrate and ligand 3: their respective acidities. More acidic ligands render the Ti center more electron deficient. Ligand 3 is a bis β-hydroxy ester, so its hydroxyls are substantially less acidic than those of tartrate, which is a bis α-hydroxy ester. The greater Lewis acidity of the metal center in 1 further activates the bidentate alkyl peroxide toward attack, facilitating the rate-determining step of the catalytic cycle: the oxygen atom transfer step in which the peroxide bond is broken. Without this extra activation, Ti–3 may be capable of rapid ligand exchange, but far less competent at oxygen atom transfer, resulting in the observed rate deceleration. A rate decrease allows other active species (such as free $Ti(OiPr)_4$) to get involved in the catalysis, complicating the system

Table II. Epoxidation Selectivity of the Ti–Ligand Complexes

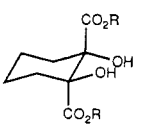
catalyst	12 (% ee)[a]	13 (% ee)[a]	14 (% ee)[b]	E/T[c]	k_{rel}[d]
$Ti(OiPr)_4$[e]	–	–	–	32/68	–
Ti–3	0	16	22	26/74	1.5
Ti–4	95	93	31	66/34	2.3
Ti–5	28	10	0	44/56	1.0
Ti–DIPT	>98	>95	>96	97/3	104

[a] The % ee of epoxy alcohol product derived from the cited allylic alcohol, yields were >85% in all cases; all epoxidations gave the same face selectivity as the analogous tartrate catalyst (last entry). [b] The % ee of unreacted allylic alcohol. [c] The erythro/threo ratio of the product epoxy alcohol. [d] Derived from the relations $k_{rel} = k_{fast}/k_{slow} = \ln(1 - C)(1 - ee)/\ln(1 - C)(1 + ee)$ where C is the fraction of consumption of the racemate and ee is % ee/100. [e] A control reaction under conditions identical with those of Ti–3, Ti–4, and Ti–5 (see Experimental Section); note lit.[1b] gives E/T 38/62.

(30) Whether the interconversion process proceeds via an intermediate in which both carbonyls are unbound at the same time is unclear and requires further study.

(31) Both the X-ray data[5] and the models of the Ti–tartrate dimer 1 suggest that the pair of facial bicyclic [2.2.1] ring systems induces a ring strain or "spring-loading" effect on the whole molecule.

(32) The concept of catalyst deactivation due to the inability to dissociate a carbonyl was supported by the results obtained using the ligand diisopropyl 1,2-dihydroxycyclohexane-1,2-dicarboxylate (15).



15

Because 15 does not allow flexing of the 5-membered Ti diolate ring to a different conformational pucker (due to the constraints of the cyclohexane backbone), we speculated that the bound carbonyl would not be able to swing away from the metal, as it can in tartrate, and thus the alkyl peroxide would not be activated by chelating η^2. The observation that a 1:1 Ti–15 catalyst showed essentially *no reaction* in the epoxidation of 12 until the mixture was warmed to room temperature, only then to produce racemic epoxy alcohol in over 24 h, seemed to confirm that this "locking in" of the carbonyl was preventing the necessary η^2-alkyl peroxide binding, and thus completely shutting down the complex's reactivity. The slow, nonselective epoxidation observed was apparently coming from free $Ti(OiPr)_4$ (observed spectroscopically in <5%): Yoshioka, M.; Sharpless, K. B., unpublished results.

and generally leading to poor net selectivity.

Resolution of these issues, particularly whether the Ti–carbonyl interaction for **3** is stronger or weaker than that for tartrate, will require further work.

The success of Ti–**4** in the asymmetric epoxidation of **12** and **13** and its virtual reproduction of the Ti–tartrate spectroscopic profile provides good evidence that it forms a catalyst species very similar to the parent and is able to mimic its asymmetry-inducing properties for primary allylic alcohols. Thus the system seems to tolerate the change from the 5-membered Ti diolate ring to the 6-membered analogue without difficulty, although apparently without eliminating all of the ring strain (it contains a pair of [3.2.1] bicyclic ring systems) since the fluxional interconversion is still observed spectroscopically at room temperature. Still, its failure to achieve effective kinetic resolution is very disturbing. Although there have been signs that the two are not always related,[33] this constitutes the first clearcut uncoupling in a complex that does not appear to involve a significant alteration in the steric environment found in the parent Ti–tartrate structure. Since we do not postulate competition from minor species (such as free $Ti(OiPr)_4$) due to the high face selectivity, this result may justify a reexamination of the working stereochemical model.[4a]

The precipitous drop in enantiomeric excess with the catalyst derived from **5** (Ti–**5**) confirms our expectations about the 7-membered Ti diolate ring. The complexity of the spectra (particularly in the presence of free alcohol) and the unusual carbonyl binding mode make it difficult to determine the structures of the species present. This, together with the intermediate molecularity indicated by the molecular weight determination, strongly suggests contributions from several species. It is speculated, then, that the poor selectivity displayed in this system may be due to one or more reactive species unrelated to **1**, with perhaps a small contribution from a 2:2 structure comparable to **1**, which could account for the analogous face selectivity relative to tartrate.

In summary, it appears that **3** forms a 2:2 Ti–L complex analogous to **1**, with a structural core which is maintained in the presence of rapid exchange of the isopropoxides, but does not readily undergo intramolecular fluxional interconversion and is not a competent epoxidation catalyst, either in a chiral or an achiral sense. Similarly, **4** also appears to form and maintain a tartrate-like 2:2 Ti–L framework in the presence of other competitive binders, but *is able* to mimic tartrate, in that it does undergo the fluxional equilibration, and is an effective and enantioselective catalyst, at least in the asymmetric epoxidation of primary allylic alcohols. In contrast, **5** appears unable to form or maintain a tartrate-like 2:2 structure to an appreciable extent, particularly in the presence of competitive binders, affording instead an ill-defined mixture which presumably contains more than one epoxidation catalyst.

Thus, both **1** and Ti–**4** show a propensity for fast fluxional interconversion, fast reaction rates, and very high enantioselectivity (despite the observation of 5–10% free $Ti(OiPr)_4$ in the latter system by NMR). On the other hand, both Ti–**3** and Ti–**15**[31] exhibit slow fluxional interconversion, very slow rate, and little or no selectivity. One is tempted to speculate on a direct correlation: whether it be due to carbonyl dissociation or something else, whatever trait compels the dimer to exhibit fluxional interconversion may also be the genesis of accelerated reaction rates, which then confers upon the system the *opportunity* to induce asymmetry. This latter point is worth emphasizing. The metal–ligand epoxidation systems which do not exhibit ligand acceleration tend to be unselective,[34] for there are almost always other species present in solution which are capable of catalyzing epoxidation, but usually in a manner which is deleterious to the overall enantiomeric excess of the product.

(33) See, for example, entries 9 and 10 of Table II and ref 4a and 7a.

Experimental Section

General. Melting points are uncorrected. IR spectra were recorded on a grating or a fourier transform infrared spectrophotometer. Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded on 300-MHz spectrophotometers, in $CDCl_3$ with TMS as an internal standard. The ^1H NMR chemical shifts are reported in units of δ relative to TMS. Optical rotations were measured using a 1-cm^3 capacity (1 dm path length) quartz cell. Elemental analyses were performed by the Robertson Laboratory, Inc., Madison, NJ; or Schwartzkopf Microanalytical Laboratory, Woodside, NY.

All reaction mixtures were stirred magnetically, unless otherwise noted. Molecular sieves (3 Å and 4 Å) were activated by heating in a vacuum oven at 160–200 °C and 0.05 mmHg for at least 8 h. Analytical thin-layer chromatography (TLC) was performed using glass plates coated with Merck silica gel 60 F-254. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh) as described by Still.[35] All oxygen- or moisture-sensitive reactions were conducted in oven-dried or flame-dried glassware under an atmosphere of dry argon or in an inert atmosphere (nitrogen) Vacuum Atmospheres drybox. Capillary gas chromatography was performed using 25–30-m fused silica capillary columns packed with SE-30 or DB-5 stationary phases.

Dichloromethane (CH_2Cl_2) was distilled from CaH_2 and stored over activated 3-Å molecular sieves prior to use; ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Pyridine was dried by sequential treatment with activated 3- or 4-Å molecular sieves. 2-Propanol was distilled from Mg onto 3-Å sieves. $Ti(OiPr)_4$ (72–73 °C, 0.8 mmHg), DET (80.5–81.0 °C, 0.04 mmHg), and DIPT (76 °C, 0.1 mmHg) were distilled under vacuum and stored under an inert atmosphere. (*E*)-(2)-Undecenol was prepared from the corresponding alkynol (Farchan Chemical Co.) by Red-Al reduction;[36] (*E*)-2,3-diphenyl-2-propenol by reduction of the acid with lithium aluminum hydride (Et_2O/0 °C); (±)-(*E*)-1-cyclohexyl-2-buten-1-ol by the addition of cyclohexylmagnesium bromide to (*E*)-2-butenal; diisopropyl 3-hexenedioate by Fisher esterification of the diacid; (±)-dimethyl 2,4-dibromoglutaric acid by the method of Ingold,[16a] the *dl* form separated from the meso as described by Velichko and coworkers;[16b] and ethyl 2(*S*)-acetoxy-3-carboxypropionate by the two-step method of Shiuey et al.[19] from (*S*)-(−)-malic acid. Unless otherwise noted, all other materials were used as received from commercial sources without further purification.

(±)-Diisopropyl 3,4-Dihydroxyadipate [(±)-3]. To a 500-mL round-bottomed flask were added **6** (114 g, 0.5 mol), 90 mL of acetone, 9 mL of H_2O, 131 mg (0.515 mmol) of solid OsO_4, and 70.3 g (0.6 mol) of solid 97% *N*-methylmorpholine *N*-oxide (NMO).[37] The resulting dark purple-red mixture became yellow

(34) For an example of ligand-decelerated catalysis in these epoxidation systems, see: Sharpless, K. B. *CHEMTECH* **1985**, 692.

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(36) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595. Jones, T. K.; Denmark, S. E. *Org. Synth.* **1986**, *64*, 182.

(37) The catalytic reaction in the presence of dihydroquinidine–*p*-chlorobenzoate (at 0.25 M) and 1 equiv of Et_4NOAc (see: Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123) afforded diol in 37% ee, and the stoichiometric reaction[14] (in toluene, at −78 °C, 0.10 M in alkaloid, H_2S quench) afforded diol with 71% ee. The enantiomeric excess was measured on the corresponding bis-MTPA ester (see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543) by both ^1H NMR and HPLC (Pirkle 1A ionic column, 1.5 mL/min, 5% iPrOH/hexane). Attempts to improve the optical purity of the enriched **3** by recrystallization from hexane resulted in enantiomer enrichments in the supernatant as the compound showed a propensity to crystallize with lowered optical enrichments (e.g., the 71% ee material crystallized to 63% ee solid and 77% ee supernatant). Several repetitions of this procedure secured material of 89% ee, $[\alpha]^{25}_D$ +26.9° (*c* 1.59, $CHCl_3$).

and homogeneous after ca. 12 h, at which time GC analysis indicated that the reaction was complete. It was quenched by the addition of 100 g of $Na_2S_2O_5$ and 200 mL of H_2O and stirred for 6 h. The mixture was diluted with 2 L of Et_2O, filtered through Celite, and washed with 200 mL of 1 N HCl, 200 mL of H_2O, and brine (2 × 200 mL). The yellow organic phase was dried (Na_2SO_4), and the solvent was evaporated to give 124.6 g (95%) of a whitish solid. One recrystallization from hexane afforded the pure product as white needles, mp 68–69 °C. For spectral data, see the procedure for the homochiral material.

Resolution Part 1. 7a: Bis(hydrogen phthalate) of (±)-3. To a 1-L round-bottomed flask equipped with magnetic stir bar and reflux condenser were added 105 g (0.40 mol) of (±)-**3**, 119 g (0.80 mol) of phthalic anhydride, and 81 mL (1.0 mol) of dry pyridine. The resulting yellow slurry was heated to 70 °C (by which time it had become homogeneous) for 20 h and then cooled to 0 °C. To the resulting hardened mass was added 120 mL of ice-cold concentrated HCl and ca. 500 mL of $CHCl_3$, the mass slowly dissolving and depositing a large crop of fluffy yellow precipitate. The solid was collected on a frit, rinsed with aqueous HCl, water, and cold $CHCl_3$, then air-dried, affording 249.6 g (111%) of crude yellow-white solid. A portion of this (137 g) was taken up in boiling CH_2Cl_2, filtered hot through cotton to remove suspended water, and then diluted with hot hexane (approximately twice the volume of the CH_2Cl_2). Upon cooling, crystallization afforded 102.1 g of white powder: mp 148 °C; IR ($CDCl_3$) 2983, 1708, 1601, 1580, 1408, 1278, 1116 cm^{-1}; ^1H NMR δ 8.07 (m, 2 H), 7.64 (m, 6 H), 5.91 (m, 2 H, C*H*O), 4.98 (h, J = 6.4 Hz, 2 H, C*H*(CH_3)$_2$), 2.88 (dd, J = 16.1, 7.7 Hz, 2 H), 2.74 (dd, J = 16.1, 6.2 Hz, 2 H), 1.14 (2d, J = 6.4 Hz, 12 H); ^{13}C NMR δ 176.0, 169.3, 165.6, 133.4, 132.8, 131.7, 131.0, 128.1, 127.4, 72.3, 68.5, 35.3, 21.4. Anal. Calcd for $C_{28}H_{30}O_{12}$: C, 60.21; H, 5.41. Found: C, 59.88; H, 5.39.

Resolution Part 2. 7b: Bis(cinchonidine salt) of 7a. To a solution of 85 g (0.153 mol) of **7a** dissolved in 1 L of hot CH_2Cl_2 in a 4-L Erlenmeyer flask, was slowly added a slurry of cinchonidine (90 g, 0.31 mol) in 2 L of hot CH_2Cl_2. The reaction mixture, which had remained yellow and homogeneous for the length of the addition, was concentrated to approximately 800 mL, and then 800–1000 mL of *tert*-butyl methyl ether (tBuOMe) was slowly added to the point of turbidity. Cooling afforded 71.4 g (42%) of white powder, which was recrystallized once more from 2:1 CH_2Cl_2–tBuOMe to 34.17 g (20%) of diastereomerically pure **7b** [analyzed following removal of the auxiliaries (vide infra) and derivitization as the bis-MTPA ester]: mp 180–184 °C; IR ($CDCl_3$) 2982, 1730, 1606, 1591, 1570, 1375, 1276, 1248, 1216, 1108 cm^{-1}; ^1H NMR (areas of interest for establishing that it is the bis salt) δ 6.45 (br s, 2 H, C*H*O of alkaloid), 5.95 (br t, 2 H, C*H*O of substrate).

(3*R*,4*R*)-Diisopropyl 3,4-Dihydroxyadipate [(+)-3]. To 30 g (26 mmol) of diastereomerically pure **7b** were added 400 mL of EtOAc and 1 L of 1 N HCl. The two homogeneous phases were separated, and the organic phase washed with 1 L of 1 N HCl, 1 L of H_2O, and 500 mL of brine. The clear solution was dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to afford homochiral **7a**, as a white solid foam (15.67 g, 107% crude).

To a solution of 15.5 g (27.8 mmol) of crude homochiral **7a** in 150 mL of dry iPrOH was added 8.0 g (28 mmol) of $Ti(OiPr)_4$ by syringe, and the solution was heated to reflux for 24 h. The reaction mixture was concentrated to a small volume and then stirred with 100 mL of 1 N HCl (affording a cloudy white precipitate) and 100 mL of CH_2Cl_2 for 2 h. The two phases were separated, and the aqueous phase was extracted with 100 mL of CH_2Cl_2. The combined organic phases were washed with 25 mL of H_2O, 25 mL of saturated aqueous $NaHCO_3$, and 25 mL of brine. After drying (Na_2SO_4) and filtering, the solvent was evaporated to afford 8.54 g of a mixture of **3** and diisopropyl phthalate. A portion of this mixture (4.4 g) was chromatographed on silica (eluent: 35% EtOAc–hexane and then 85%) to give 2.64 g of white solid product. The derived bis-MTPA ester of the crude product revealed the material to be enantiomerically pure within the limits of detection by HPLC and ^1H NMR (see ref 37 for conditions). A portion of the solid was recrystallized twice from hexane to give analytically pure **3**: mp 64.0–64.5 °C; $[\alpha]^{25}_D$ +31.3° (c 1.48, $CHCl_3$); IR ($CDCl_3$) 3561, 2984, 2937, 1720, 1467, 1455, 1376, 1278, 1182, 1106, 956 cm^{-1}; ^1H NMR δ 5.06 (h, J = 6.5 Hz, 2 H), 3.97 (m, 2 H, C*H*O), 3.35 (d, J = 5.2 Hz, 2 H, OH), 2.64 (dd, J = 16.0, 8.4 Hz, 2 H), 2.54 (dd, J = 16.0, 4.7 Hz, 2 H), 1.26 (d, J = 6.5 Hz, 12 H); ^{13}C NMR δ 172.1, 70.0, 68.3, 38.3, 21.7. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.87; H, 8.46.

Only the recrystallized material was used in subsequent studies.

(±)-2,4-Dihydroxyglutaric Acid [(±)-8]. Racemic **8** was prepared from (±)-dimethyl 2,4-dibromoglutarate (44.0 g, 0.138 mol) by treatment with 5 N NaOH in MeOH according to the procedure of Darby,[38] affording 24.5 g (ca. 85–90%) of a white solid, which was a mixture of (±)-**8** and its γ-lactone: mp 134–137 °C; IR (CH_2Cl_2) 3680, 3570, 2850, 1800, 1740, 1712, 1600 cm^{-1}. The mixture was recrystallized from acetone to afford pure (±)-**8**: mp 143–144 °C; ^1H NMR (DMSO-d_6) δ 4.1 (dd, J = 5.9, 7.8 Hz, 2 H), 3.3 (br, 4 H), 1.8 (dd, J = 6.0, 7.8 Hz, 2 H); ^{13}C NMR (DMSO-d_6 + D_2O) δ 176.2, 66.4, 38.8; LRMS m/z 165 (M^+), 147, 119, 101, 73. Anal. Calcd for $C_5H_8O_6$: C, 36.59; H, 4.92. Found: C, 36.74; H, 4.90.

9: Monobrucine Salt of (±)-2,4-Dihydroxyglutaric Acid. A hot solution of (±)-**8** (22.8 g, 0.14 mol) dissolved in 50 mL of water was added to a hot solution of brucine (52.0 g, 0.14 mol) dissolved in 300 mL of acetone–water (3:1) and stirred vigorously. The clear mixture was filtered hot, and on standing a white, crystalline precipitate formed which was removed by filtration and dried under vacuum to give 28.5 g of **9**. The salt was recrystallized five times from water to give 2.71 g (4%) of the diasteriomerically pure monobrucine salt **9** (analyzed as described below, by removal of the auxiliary to give **4** and comparison of the derived bis-MTPA ester to that of the racemate): mp 209–212 °C; $[\alpha]^{25}_D$ −27.5° (c 1.8, H_2O); ^1H NMR (250 MHz, DMSO-d_6) δ 7.67 (s, 1 H), 7.05 (s, 1 H), 6.15 (br m, 1 H), 4.65 (m, 1 H), 4.5–4.25 (m, 3 H), 4.2–3.8 (m, 5 H), 3.75 (d, J = 4.5 Hz, 6 H), 3.6–3.4 (m, 1 H), 3.3–3.05 (m, 2 H), 3.05–2.85 (m, 3 H), 2.05–1.8 (m, 3 H), 1.6–1.25 (m, 2 H). The absolute configuration was assigned as 2*S*,4*S* by correlation to the derived barium salt of the acid: $[\alpha]^{25}_D$ −12.5° (c 0.72, H_2O); lit.[39] $[\alpha]^{25}_D$ −30.9° (c 1.0, H_2O).

(2*S*,4*S*)-Diisopropyl 2,4-Dihydroxyglutarate [(−)-4]. A sample of diastereomerically pure **9** (0.41 g, 0.76 mmol) was dissolved in 100 mL of anhydrous methanol. An ethereal solution of diazomethane was added until a strong yellow color persisted, indicating an excess of reagent. After removal of the methanol in vacuo, flash chromatography (100% ethyl acetate eluent) provided 0.097 g (ca. 66%) of a 12:1 mixture of the methyl ester and corresponding γ-lactone. The reaction was similarly performed on up to 2.0 g (3.71 mmol) of the pure salt with proportionate mass recovery, and the product was taken on directly.

A 50-mL round-bottomed flash equipped with stir bar and reflux condenser was charged with 1.25 g of the above product mixture (ca. 6.5 mmol) and 100 mL of 2-propanol. Two drops of $Ti(OiPr)_4$ were added, and the mixture was refluxed for 1.5 h. The reaction was then cooled to room temperature, and the isopropyl alcohol removed in vacuo. The residue was dissolved in dichloromethane and washed with 10% tartaric acid. Column chromatography (20% ethyl acetate–hexane) afforded 1.31 g (92%) of (−)-**4** as a pale yellow solid. Recrystallization from hexane yielded 1.01 g (62%) of a white, flocculent solid (analysis of the bis-MTPA ester by ^1H NMR showed >95% ee): mp 66–67 °C; $[\alpha]^{25}_D$ −8.8° (c 3.0, $CHCl_3$); ^1H NMR δ 5.12 (h, J = 6.2 Hz, 1 H), 4.36 (m, 2 H), 2.98 (d, J = 5.2 Hz, 2 H), 2.1 (dd, J = 5.7 Hz, 5.2 Hz, 2 H), 1.29 (d, J = 6.2 Hz, 12 H); ^{13}C NMR (300 MHz) δ 174.3, 69.6, 67.4, 37.9, 21.7; IR ($CDCl_3$) 3530, 2585, 1725, 1470, 1377, 1265, 1105, 840 cm^{-1}. Anal. Calcd for $C_{11}H_{20}L_6$: C, 53.20; H, 8.13. Found: C, 52.80; H, 8.15.

Kolbe Electrolysis of (−)-10. To a 500-mL three-necked round-bottomed flask were added 200 mL of dry ethanol and 1.3 g (0.057 mol) of metallic sodium. The resulting mixture was gently warmed until homogeneous and then was added to a solution of

(38) Darby, N. Ph.D. Dissertation, University of Alberta, Edmonton, Alberta, 1972.

(39) Benoiton, L.; Winitz, M.; Birnbaum, S. M.; Greenstein, J. P. *J. Am. Chem. Soc.* **1957**, *79*, 6192. The source of the discrepancy in the magnitude of the two rotations is unclear since the material prepared here was shown to be homochiral. The observation of very high enantioselectivity for the same olefin face by Ti–(−)-**4** and (2*S*,3*S*)-DIPT in the asymmetric epoxidation might be used as further confirmation of the cited 2*S*,4*S* stereochemical assignment.

10.2 g (0.05 mol) of (-)-10 in 200 mL of dry ethanol. This solution was transferred to an electrolysis apparatus (containing ca. 50 mL of mercury cathode) built as described by Dinh-Nguyen[40] with the exception that the Pt anode mesh was suspended in the solution by attachment to a glass rod and passivation of the electrode was diminished by bubbling a stream of argon gas above the mesh, not by mechanical stirring with a hollow rod containing mercury and Pt wire, as was described.[40] The electrolysis was carried out in much the same way as was described by Brettle and Latham,[18] except that it was initiated at 40 V and 0.2 A (instead of 100 V and 5 A as described) and then run at constant current until the potential had risen to approximately 250 V (ca. 16 h). The Na/Hg amalgam was drained through the bottom of the apparatus, and the remaining reaction solution was evaporated to a yellow oil, which was dissolved in a solution of ether and saturated aqueous sodium bicarbonate. The two phases were separated, and the organic phase was washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated to 3.15 g (54% crude) of a viscous yellow-tinted oil, which was composed mainly of one product, assigned as the dihydroxy diethyl ester **11**.[20] The product was not further purified but was taken on directly.

(2*S*,5*S*)-Diisopropyl 2,5-Dihydroxyadipate [(-)-5]. To a flame-dried 100-mL round-bottomed flask were added 2.07 g (ca. 8.8 mmol) of the crude electrolysis product **11**, 40 mL of dry 2-propanol, and 2.49 g (8.8 mmol) of $Ti(OiPr)_4$. The solution was heated to gentle reflux under argon for ca. 16 h and then cooled to room temperature, concentrated to a small volume, diluted with CH_2Cl_2, and quenched with ca. 50 mL of 1 M HCl. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were washed with a minimum amount of water, saturated aqueous sodium bicarbonate, and brine, dried ($MgSO_4$), filtered, and concentrated to afford 1.69 g (ca. 73%) of a white solid. Recrystallization from hexane afforded 956 mg of flocculent white crystals: mp 53.5–54.5 °C; $[\alpha]^{25}_D$ -17.3° (*c* 1.6, $CHCl_3$); IR (CH_2Cl_2) 3540, 2980, 2940, 2280, 1725, 1470, 1450, 1390, 1380, 1290–1190, 1150, 1105 cm^{-1}; ^1H NMR δ 5.13 (m, 2 H, C*H*$(CH_3)_2$), 4.20 (m, 2 H, C*H*OH), 3.03 (d, *J* = 5.5 Hz, 2 H, OH), 2.1–1.7 (m, 4 H), 1.31 (2 d, *J* = 6.3, 6.4 Hz, 12 H, CH_2); ^{13}C NMR δ 174.4, 70.0, 69.7, 29.7, 21.7, 21.7. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.96; H, 8.46. Found: C, 54.88; H, 8.18.

Comparison of the derived bis-MTPA ester with racemate showed >95% ee. The absolute configuration was confirmed as 2*S*,5*S* by correlation of the derived diacetate: $[\alpha]^{25}_D$ -31.2° (*c* 1.71, $CHCl_3$) [lit.[18] $[\alpha]^{25}_D$ -31.1° (*c* 6.2, $CHCl_3$) for 2*S*,5*S*].

General Procedure for Asymmetric Epoxidation of 12 or 13 Using Ligands 3, 4, or 5. To a dry 5-mL round-bottomed flask were added **3**, **4**, or **5** (0.137 mmol), 0.5 mL of dichloromethane, ca. 25 mg of 3-Å powdered molecular sieves, and **12** or **13** (0.114 mmol). After cooling the mixture to 0 °C, $Ti(OiPr)_4$ (33 mg, 0.114 mmol) was added via syringe, and the resultant solution was "aged" for 20 min.[2b] The reaction was further cooled to -20 °C, and anhydrous *tert*-butyl hydroperoxide (5.7 M in dichloromethane, 40 μL, 0.228 mmol) was added. After reaching completion (TLC), the reaction was quenched with 3 mL of 20% tartaric acid/ferrous sulfate solution, then 5 mL of water and 10 mL of dichloromethane were added, and the two phases were separated. The organic phase was extracted with brine, dried ($MgSO_4$), filtered, and concentrated. In some cases, the residue was dissolved in ether and stirred for 20 min with 10% NaOH–saturated NaCl solution to hydrolyze the ligand, or, alternatively, the ligands and products were isolated by column chromatography. If the former procedure was followed, the two phases were separated, and the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford to epoxy alcohol. For the product derived from **11**, direct HPLC analysis of the epoxy alcohol (Pirkle 1A phenyl glycine ionic column, 3% isopropyl alcohol–hexane, 5 mL/min) allowed determination of the enantiomeric excess. For the epoxy alcohol derived from **12**, analysis of the enantiomeric excess was accomplished by ^1H NMR analysis (in C_6D_6) of the derived MTPA ester.

Kinetic Resolution of (*E*)-1-Cyclohexyl-2-buten-1-ol (14) Using Ligands 3, 4, or 5. A 5-mL round-bottomed flask was charged with **14** (42 mg, 0.27 mmol), **3**, **4**, or **5** (0.32 mmol), 10 μL of n-$C_{15}H_{32}$ (to monitor percent conversion by GC), ca. 25 mg of 3-Å powdered molecular sieves, and 1.0–1.5 mL of dichloromethane, and cooled to 0 °C. $Ti(OiPr)_4$ (77 mg, 0.27 mmol) was added by syringe, and the resulting pale yellow solution was stirred for 20 min at 0 °C under inert (argon) atmosphere. The solution was then cooled to -20 °C whereupon a t_0 aliquot (100 μL) was removed and quenched with two drops of 10% ferrous sulfate–tartaric acid and ether. Anhydrous *tert*-butyl hydroperoxide (5.7 M in CH_2Cl_2, 29 μL, 0.165 mmol) was added by syringe. When the reaction reached approximately 55–65% conversion (GC), it was quenched with 10% ferrous sulfate–tartaric acid and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. As above, in cases where the ligand was directly hydrolyzed, 15 mL of ether and 5 mL of 10% NaOH–brine were added, and the mixture was stirred for 25 min. The aqueous layer was extracted with ether (2 × 10 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Column chromatography (20% ethyl acetate–hexane) separated the epoxy and allylic alcohols. The enantiomeric excess of the allylic alcohol was determined by ^1H NMR analysis of the acetate using Eu(hfc)$_3$ in C_6D_6, and by ^1H NMR analysis of the derived MTPA ester. The erythro/threo ratio of the epoxy alcohol was determined by GC (DB-5 column) and checked by ^1H NMR and GC analysis of the derived epoxy acetates.

Spectroscopy of the Alcohol-Free 1:1 $Ti(OiPr)_4$–Ligand Mixtures. Ligands **3**, **4**, or **5** (0.21 mmol) and $Ti(OiPr)_4$ (60 mg, 0.21 mmol) were combined in CH_2Cl_2 in the drybox, and the solvent was removed in vacuo. Addition of dichloromethane and evaporation was repeated three more times to insure removal of the released 2-propanol. The clear, glassy compounds remaining were dissolved in CD_2Cl_2 or $CDCl_3$ for spectral analysis.

[Ti(3)(OiPr)$_2$]$_2$: IR ($CDCl_3$) 2975, 2932, 2868, 1717, 1688, 1467, 1454, 1375 cm^{-1}; ^1H NMR δ 5.06 (h, *J* = 6.4 Hz, 2 H, iPr ester: C*H*$(CH_3)_2$), 4.95 (h, *J* = 6.4 Hz, 2 H, iPr ester: C*H*$(CH_3)_2$), 4.78 (m, 2 H, ligand C*H*O), 4.70 (h, *J* = 6.5 Hz, 2 H, Ti–OiPr: C*H*$(CH_3)_2$), 4.58 (h, *J* = 6.5 Hz, 2 H, Ti–OiPr: C*H*$(CH_3)_2$), 4.41 (m, 2 H, ligand C*H*O), 2.84 (br d, *J* = 6.8 Hz, 4 H, 2 CH_2), 2.70 (dd, *J* = 11.5, 6.0 Hz, 2 H, CH_2), 2.58 (dd, *J* = 11.5, 5.6 Hz, 2 H, CH_2), 1.20 (m, 48 H, CH_3); ^{13}C NMR (CD_2Cl_2) δ 173.3, 171.2, 88.2, 83.3, 78.8, 77.5, 68.9, 68.1, 41.7, 41.2, 26.1, 26.0, 25.9, 22.1, 22.0.

[Ti(4)(OiPr)$_2$]$_2$: IR (CD_2Cl_2) 2980, 2935, 2870, 2620, 1730, 1780, 1645, 1470, 1455, 1428, 1375, 1355, 1330, 1285, 1265 cm^{-1}; ^1H NMR (250 MHz, CD_2Cl_2) δ 5.3 (s, 2 H), 5.2–4.9 (br, 6 H), 4.8–4.6 (m, 4 H), 2.4–2.2 (br m, 4 H, CH_2), 1.4–1.1 (br m, 48 H, CH_3); ^{13}C NMR (CD_2Cl_2) δ 177.4, 173.2, 78.4, 77.1, 77.0 br, 76.95 br, 76.9 br, 76.5, 72 br, 68 br, 38.4, 26.7, 25.6, 21.9.

Ti-5:[41] IR ($CDCl_3$) 2971, 2931, 2865, 1738, 1712, 1672, 1466, 1454, 1376, 1164, 1125, 999 cm^{-1}; ^1H NMR δ 5.12 (m, 2 H), 4.95–4.85 (m, 1 H), 4.85–4.65 (m, 1 H), 4.50 (weak m), 2.07 (m, 2 H), 1.80 (m, 1 H), 1.20 (m, 16 H); ^{13}C NMR δ 186.0, 80.5 br, 76.5 br, 71.8, 68.8 br, 31.2 br, 26.5–25.0 br, 21.7, 21.6.

Determination of Molecular Weight[22] of 1:1 $Ti(OiPr)_4$–Ligand Mixtures. Ligands **3**, **4**, or **5** (0.437 mmol) and $Ti(OiPr)_4$ (0.124 g, 0.437 mmol) were combined in CH_2Cl_2 in the drybox, and the solvent was removed in vacuo. The addition of solvent and removal of volatiles was repeated three times more as for the spectroscopy samples; the clear, glassy material was then dissolved in CH_2Cl_2 and placed in one side of a glass molecular weight apparatus built to allow ready passage of vapor from one bulb to the other. The standard, n-Bu_4Sn (0.152 g, 0.437 mmol), was dissolved in CH_2Cl_2 and placed in the other side of the molecular weight apparatus. The apparatus was cooled in a liquid nitrogen bath, placed under vacuum for several minutes, and then closed off to the vacuum and allowed to warm to room temperature. This freeze–pump–thaw degassing cycle was repeated twice more, and then the apparatus was allowed to equilibrate under isothermal conditions over 7–20 days. The molecularity, *n*, was determined by the equation:

$$n = \text{molecular weight observed}/\text{molecular weight calcd for monomer}$$

(40) Dinh-Nguyen, N. *Acta Chim. Scand.* **1958**, *12*(3), 585.

(41) Since the structural composition is unassigned for this complex only normalized integration values are presented with the ^1H NMR data.

The molecular weight observed (MW_{obsd}) was determined by the equation:

$$MW_{obsd} = (g_{sample})(MW_{ref})(V_{ref})/(g_{ref})(V_{sample})$$

where g = mass and V = volume at equilibrium.

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Cycloadditions of (Arylalkylamino)ketenes with Cycloalkenes

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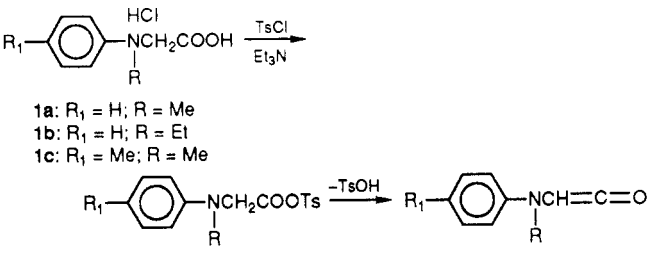
(Arylalkylamino)ketenes were prepared from the corresponding glycine derivatives and underwent in situ cycloadditions with cyclopentadiene, cycloheptene, and cyclooctene to yield only the *endo*-bicyclocyclobutanones. The cycloheptene and cyclooctene cycloaddition products underwent dehydrogenation under the reaction conditions to yield bicyclo enamines. A mechanism is proposed for this dehydrogenation involving a radical cation of the phenylalkylamine. (Phenylmethylamino)methylketene was also prepared and found to undergo an intramolecular Friedel–Crafts-type acylation to yield an indole derivative when prepared by the acetic anhydride–sodium acetate method.

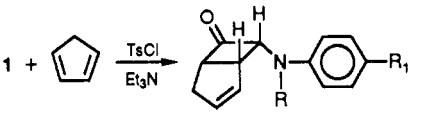
The stereospecific [2 + 2] ketene cycloaddition to alkenes is a valuable method to synthesize cyclobutanones and related compounds.[1] Ketenes bearing heteroatoms adjacent to the ketene functionality such as chlorine, oxygen, and sulfur show an increased reactivity in cycloaddition reactions and have been successfully used in many syntheses of cyclic compounds. However, there are only a few scattered reports on the chemistry of aminoketenes and these reports are limited to aminoketenes in which the nitrogen atom was substituted by an electron-withdrawing substituent such as succinoyl, maleyl, or phthaloyl groups.[2] The aminoketenes were prepared by the dehydrohalogenation of amino acid chlorides and used in the synthesis of penicillin-like β-lactams by cycloaddition with imines. The existence of aminoketenes under such conditions is questioned because of an alternative pathway to explain the formation of the β-lactams.[3] We report a one-pot preparation of (arylalkylamino)ketenes and the trapping of such ketenes with different cycloalkenes.

The starting compounds for this study are *N*-aryl-*N*-alkylglycine hydrochlorides. The use of (disubstituted-amino)ketenes is based on avoiding the possible reaction between a primary or secondary amino group with the ketene functionality. The conventional method of generating the (arylalkylamino)ketenes from the acid chlorides was unsuccessful. Therefore, *p*-toluenesulfonyl chloride was selected as the reagent for generation of the ketenes. The amino acid hydrochloride was treated with *p*-toluenesulfonyl chloride and an excess of triethylamine to form the mixed anhydride, which, based on our previous work,[4] could eliminate *p*-toluenesulfonic acid to generate the (arylalkylamino)ketene (Scheme I).

Scheme I

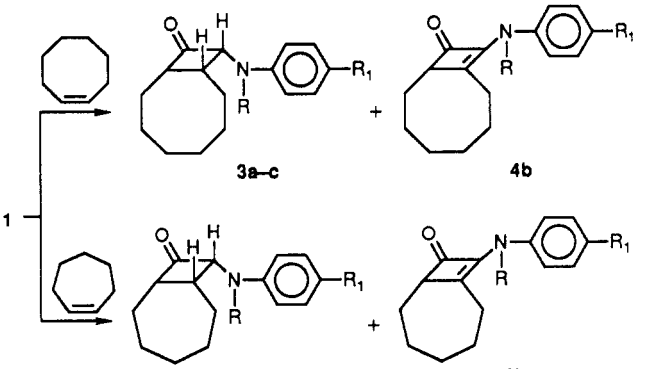


Scheme II



2a: R_1 = H; R = Me
2b: R_1 = H; R = Et
2c: R_1 = Me; R = Me

Scheme III



3a, 5a: R = Me; R_1 = H
3b, 4b, 5b, 6b: R = Et; R_1 = H
3c, 5c: R = Me; R_1 = Me

The reaction mixture of *N*-aryl-*N*-alkylglycine hydrochlorides with 1.2 to 1.5 equiv of *p*-toluenesulfonyl chloride, 5 equiv of olefin, and triethylamine in benzene is a dark red solution containing some insoluble salts (Scheme II).

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